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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **DIETARY SUPPLEMENT ENHANCING THE MUSCULAR ENERGY METABOLISM, COMPRISING AN ALKAN-NOYL CARNITINE AND RIBOSE**

(57) Abstract: A health food/dietary supplement is disclosed suitable for enhancing muscular energy metabolism, comprising as its characterising active ingredients an alkanoyl L-carnitine and ribose.

Dietary supplement enhancing the muscular energy metabolism,
comprising an alkanoyl carnitine and ribose

The present invention relates to a health food/dietary supplement comprising as its characterising ingredients an alkanoyl L-carnitine selected from the group consisting of isovaleryl L-carnitine and propionyl L-carnitine or their pharmacologically acceptable salts or mixtures of the same and a monosaccharide pentose, particularly ribose or its phosphorylated analogues.

It has been found that the above-mentioned composition is extremely effective in exerting a potent stimulation of muscular energy metabolism, and can thus be profitably used in the prevention of myocardial insufficiency and in post-infarct conditions, as well as in the course of prolonged muscular effort during physical and sporting exercises, owing to the unexpected synergistic effect exerted by its components.

Isovaleryl L-carnitine, a natural component of the pool of carnitines, presents specific activity at lysosomal level and on the cytosolic movements of calcium. It is therefore capable of intervening in proteolytic processes such as occur during intense, prolonged effort and of protecting a number of organs, such as the liver, against the action of toxic substances.

Propionyl L-carnitine exerts an intense antioxidant effect and is particularly effective in enhancing the peripheral circulation and cardiac functional capacity.

Moreover, muscular carnitine transferase possesses a greater affinity for propionyl L-carnitine than for L-carnitine, and consequently propionyl L-carnitine possesses a higher degree of specificity for cardiac and skeletal muscle. In addition, propionyl L-carnitine transferase, transporting the propionyl group, increases the uptake of this component by the muscle cells, which may be of particular importance

for energy purposes, in that the propionate can be used by the mitochondria as an anapleurotic substrate and provide energy in the absence of oxygen.

Equally well known are the metabolic effects of ribose. Ribose is a monosaccharide pentose which is important in the body for the synthesis of nucleotides and other metabolic products. It is formed by conversion of glucose via the pentose phosphates. In the presence of a ribokinase ribose is phosphorylated to ribose-5-phosphate which, through the production of 5-phosphoribosyl-1-pyrophosphate (PRPP), can be used for the synthesis of nucleotides necessary for the production of ATP. PRPP, in addition to intervening in the production of ATP, is also important for the synthesis of nucleotides such as adenine and hypoxanthine and of ribonucleotides and deoxyribonucleotides.

It has now been found surprisingly that a composition comprising a combination of the following as its characterising components:

(a) an alkanoyl L-carnitine selected from the group comprising isovaleryl L-carnitine, propionyl L-carnitine or their pharmacologically acceptable salts or mixtures of the same; and

(b) ribose or a phosphorylate derivative thereof, constitutes an effective health food/dietary supplement for the prevention of states of myocardial or skeletal muscle dysfunction related to conditions of anoxia or insufficient energy supply as occurring in coronary or post-infarct disorders or during prolonged physical activity and muscle fatigue, owing to the potent and unexpected synergistic effect exerted by its components.

The dietary supplement according to the present invention may additionally contain

(c) a "carnitine" selected from the group comprising L-carnitine, acetyl L-carnitine, butyryl L-carnitine and valeryl L-carnitine, or their pharmacologically acceptable salts or mixtures of the same.

The weight-to-weight ratios of the above-mentioned components (a):(b):(c) range from 1:1:1 to 1:10:2.

The surprising synergistic effect achieved with the combination of "carnitines" (term denoting collectively both L-carnitine and the alkanoyl L-carnitines), particularly isovaleryl L-carnitine and/or propionyl L-carnitine, and ribose, has been demonstrated by several pharmacological tests (some of which are described here below) chosen in such a way as to prove strongly predictive for the purposes of the practical use of this composition in the preventive/nutritional/dietetic field.

In particular, this unexpected synergistic effect on the increase in energy capabilities at both cardiac and muscular level exerted by the combination according to the present invention enables it to be used in the prevention of both myocardial insufficiency and of muscle fatigue such as occur in cases of myocardial ischaemia or in the course of intense muscular effort due to prolonged physical exercise or sporting activity.

Test of ATP concentrations in heart subjected to anoxia

In this test the technique adopted was the one using papillary muscle of rabbit heart perfused and subjected to anoxia which, as is known, leads to an impoverishment of its ATP energy reserves. With this test, the aim was to observe whether or not preventive treatment with isovaleryl L-carnitine, with propionyl L-carnitine, with a carnitine combination or with ribose, or with a combination of these was capable of protecting cardiac muscle against the loss of ATP induced by anoxia.

In this test, a batch of New Zealand rabbits was used, subdivided into different groups which were injected intravenously every day for three consecutive days with isovaleryl L-carnitine alone (100 mg/kg), propionyl L-carnitine alone (100 mg/kg) or a carnitine combination consisting of propionyl L-carnitine (25 mg/kg), acetyl L-carnitine (25

mg/kg), L-carnitine (25 mg/kg), and isovaleryl L-carnitine (25 mg/kg) or with ribose alone (100 mg/kg), or ribose combined with the above-mentioned "carnitines".

At the end of the third day of treatment, all the animals were sacrificed and their hearts excised. Sections of papillary muscle measuring 1 mm in diameter and 4-5 mm in thickness were isolated from the excised hearts. The isolated papillary muscle was perfused in a thermostatic bath with a saturated 100% O₂ solution.

The anoxic state was obtained by introducing 100% N₂ instead of O₂ into the bath. For the measurement of the ATP concentrations in the papillary muscle the method described by Strehler was adopted (Strehler B.L. Methods in Enzymology 111 N.Y. Acad. Press., 879, 1957).

The analysis was carried out on tissue samples maintained in conditions of perfusion with oxygen for 90 minutes and after a period of anoxia of the same duration.

The results of this test, presented in Table 1, indicate that propionyl L-carnitine, isovaleryl L-carnitine, the carnitine combination and ribose are individually capable of partly protecting the ATP present in papillary muscle against anoxia, but that it was only with the combination of propionyl L-carnitine or isovaleryl L-carnitine plus ribose or with the combination of the carnitine combination plus ribose that complete protection against the anoxia-induced reduction in ATP could be obtained, thus demonstrating the potent synergistic effect exerted by the components of the combination.

Table 1

Test of ATP concentrations in papillary muscle of heart subjected to hypoxia

Treatment	ATP concentration (mol/g tissue)	
	Before hypoxia	After hypoxia
Controls	1.60±0.55	0.41±0.055
Isovaleryl L-carnitine	1.50±0.60	0.55±0.65
Propionyl L-carnitine	1.64±0.79	0.60±0.040
Carnitine combination	1.55±0.50	0.62±0.060
Ribose	1.62±0.39	0.55±0.075
Isovaleryl L-carnitine + ribose	1.50±0.25	1.15±0.055
Propionyl L-carnitine + ribose	1.61±0.45	1.25±0.35
Carnitine combination + ribose	1.65±0.60	1.16±0.30

Experimental myocardial anoxia test

Adopting the technique described by Selych (Selych et al., Angiology, 11, 398, 1960) and modified by Clark (Clark C., J. Pharmacol. Methods, 3, 357, 1980), these tests were used to evaluate the protective activity of isovaleryl L-carnitine, propionyl L-carnitine, carnitine combination, ribose and various combinations of the same against ventricular arrhythmias induced by left coronary ligation in the rat.

Coronary occlusion and the resulting myocardial anoxia lead, after 5-8 minutes, to the onset of arrhythmias. In these tests, ventricular ectopic contractions were counted for a period of 30 minutes after ligation both in control rats and in rats that had received slow injections into the left ventricle, 15 minutes before ligation, of a solution containing isovaleryl L-carnitine alone (100 mg/kg), propionyl L-carnitine alone (100 mg/kg), or carnitine combination alone consisting of propionyl L-carnitine (25 mg/kg), acetyl L-carnitine (25 mg/kg) and isovaleryl L-carnitine (25 mg/kg) or ribose alone (100 mg/kg), or a combination of ribose plus isovaleryl L-carnitine or propionyl L-carnitine or a combination of ribose plus carnitine combination at the doses described above.

The results of this test (Table 2) indicate that, whereas isovaleryl L-carnitine alone or propionyl L-carnitine alone or carnitine combination alone or ribose alone produce only slight reductions in the number of ectopic contractions compared to controls, such contractions are reduced almost to the extent of disappearing altogether when ribose is injected in combination with isovaleryl L-carnitine, or propionyl L-carnitine, or carnitine combination, thus demonstrating the potent and unexpected synergistic effect exerted by the combination according to the present invention.

Table 2

Test of arrhythmia induced by myocardial anoxia

Treatment	Start of arrhythmias after (min)	No. of ectopic contractions during 30 minutes after ligation
Controls	5 - 7	989±96
Isovaleryl L-carnitine	5 - 7	860±75
Propionyl L-carnitine	5 - 8	830±86
Carnitine combination	5 - 8	810±99
Ribose	5 - 7	855±110
Isovaleryl L-carnitine + ribose	6 - 7	270±95
Propionyl L-carnitine + ribose	6 - 8	230±112
Carnitine combination + ribose	6 - 8	207±93

Some non-limiting examples of compositions according to the present invention are given hereinbelow:

Lozenges, capsules, tablets

- | | | |
|----|------------------------|--------|
| 1) | Propionyl L-carnitine | 500 mg |
| | Ribose | 500 mg |
| 2) | Isovaleryl L-carnitine | 500 mg |
| | Ribose | 500 mg |

3)	Propionyl L-carnitine	125 mg
	Acetyl L-carnitine	125 mg
	L-carnitine	125 mg
	Isovaleryl L-carnitine	125 mg
	Ribose	500 mg

Granulates or vials

4)	Propionyl L-carnitine	1 g
	Ribose	1 g
5)	Isovaleryl L-carnitine	1 g
	Ribose	1 g
6)	Propionyl L-carnitine	1 g
	Ribose	2,5 g
7)	Propionyl L-carnitine	250 mg
	Acetyl L-carnitine	250 mg
	Isovaleryl L-carnitine	250 mg
	L-carnitine	250 mg
	Ribose	2,5 g
8)	Propionyl L-carnitine	250 mg
	Acetyl L-carnitine	250 mg
	Isovaleryl L-carnitine	250 mg
	L-carnitine	250 mg
	Ribose	2 g
	Ribonucleic acid	100 mg
	Deoxyribonucleic acid	100 mg
9)	Propionyl L-carnitine	250 mg
	Acetyl L-carnitine	250 mg
	Isovaleryl L-carnitine	250 mg
	L-carnitine	250 mg
	Ribose	2 g
	L-glutamine	100 mg
	L-alanine	100 mg
	L-arginine	100 mg

	L-glicine	100 mg
	L-histidine	100 mg
	L-isoleucine	100 mg
	L-phenylalanine	50 mg
	L-threonine	50 mg
	L-serine	100 mg
10)	Propionyl L-carnitine	250 mg
	Acetyl L-carnitine	250 mg
	Isovaleryl L-carnitine	250 mg
	L-carnitine	250 mg
	Ribose	1 g
	Destrose	0,5 g
	Fructose	0,5 g
	Maltose	0,5 g
11)	Propionyl L-carnitine	250 mg
	Acetyl L-carnitine	250 mg
	Isovaleryl L-carnitine	250 mg
	L-carnitine	250 mg
	Ribose	1 g
	Glucose-1,6-diphosphate	200 mg
	Fructose-1,6-diphosphate	200 mg
	Galactose-1,6-phosphate	200 mg
	Glycerol-3-phosphate	200 mg
	Phosphoenolpyruvate	100 mg
	Thiamine pyrophosphate	5 mg
	Pyridoxal-5-phosphate	5 mg
	Magnesium stearate	2 mg
12)	Propionyl L-carnitine	250 mg
	Acetyl L-carnitine	250 mg
	Isovaleryl L-carnitine	250 mg
	L-carnitine	250 mg
	Ribose	1 g
	Vit. A	1250 U.I.
	Vit. B ₁	0,5 mg

Vit. B ₆	30 mg
Vit. C	50 mg
Vit. E	5 mg
Nicotinammide	25 mg
Vit. B ₁₂	100 mcg
Vit. D	100 U.I.
Pantothenic acid	30 mg
Magnesium glycinate	5 mg
Manganese	1 mg
L-Selenomethionine	50 mcg
Molybdenum	10 mcg
Zinc	1 mg

What is meant by a pharmacologically acceptable salt of the various carnitines mentioned in the present invention, is, in addition to the respective inner salts, any salt of these with an acid which does not give rise to unwanted toxic or side effects. These acids are well known to pharmacologists and to experts in pharmaceutical technology.

Non-limiting examples of such salts are the following: chloride; bromide; iodide; aspartate, acid aspartate; citrate, acid citrate; tartrate; phosphate, acid phosphate; fumarate, acid fumarate; glycerophosphate; glucose phosphate; lactate; maleate, acid maleate; mucate; orotate; oxalate, acid oxalate; sulphate, acid sulphate; trichloroacetate; trifluoroacetate and methane sulphonate.

Among these salts, isovaleryl L-carnitine acid fumarate (US 5,227,518) is particularly preferred.

A list of FDA-approved pharmacologically acceptable acids is given in Int. J. Pharm., 33, 1986, 201-217, the latter publication being incorporated in the present specification by reference.

The supplement of the invention may further comprise vitamins, coenzymes, mineral substances, aminoacids and antioxidants. The

supplement may be manufactured in the form of tablets, lozenges, capsules, pills, granulates, syrups, vials or drops.

Claims

1. A food/dietary supplement which comprises the following characterizing ingredients:
 - (a) an alkanoyl L-carnitine selected from the group comprising isovaleryl L-carnitine, propionyl L-carnitine or the pharmacologically acceptable salts thereof or mixtures thereof; and
 - (b) ribose or a phosphorylate derivative thereof.
2. The supplement of claim 1, further comprising:
 - (c) a "carnitine" selected from the group comprising L-carnitine, acetyl L-carnitine, butyryl L-carnitine and valeryl L-carnitine or the pharmacologically acceptable salts or mixtures thereof.
3. The supplement of anyone of the preceding claims which further comprises vitamins, sugars, coenzymes, mineral substances, aminoacids, peptides and antioxidants.
4. The supplement of any of the preceding claims wherein the pharmacologically acceptable salt is selected from the group comprising: chloride; bromide; iodide; aspartate, acid aspartate; citrate, acid citrate; tartrate; phosphate, acid phosphate; fumarate, acid fumarate; glycerophosphate; glucose phosphate; lactate; maleate, acid maleate; mucate; orotate; oxalate; acid oxalate; sulphate, acid sulphate; trichloroacetate; trifluoroacetate and methane sulphonate.
5. The supplement of any of the preceding claims, for the prevention of myocardial insufficiency and in post-infarct conditions, psychomotor alterations and to cope with the increased muscular energy requirements.
6. A food/dietary supplement in solid, semi-solid or liquid form.

7. The food/dietary supplement of any of the preceding claims in the form of tablets, capsules, lozenges, pills, granulates, creams, syrups or drops.

8. The supplement of any of the preceding claims, wherein the weight ratio of ingredients (a):(b):(c) ranges from 1:1:1 to 1:10:2.

9. The supplement of claim 8, in unit dosage form, comprising:

Propionyl L-carnitine	125 mg
Acetyl L-carnitine	125 mg
L-carnitine	125 mg
Isovaleryl L-carnitine	125 mg
Ribose	500 mg

10. The supplement of claim 8, in unit dosage form, comprising:

Propionyl L-carnitine	250 mg
Acetyl L-carnitine	250 mg
Isovaleryl L-carnitine	250 mg
L-carnitine	250 mg
Ribose	2 g
Ribonucleic acid	100 mg
Deoxyribonucleic acid	100 mg

11. The supplement of claim 8, in unit dosage form, comprising:

Propionyl L-carnitine	250 mg
Acetyl L-carnitine	250 mg
Isovaleryl L-carnitine	250 mg
L-carnitine	250 mg
Ribose	2 g
L-glutamine	100 mg
L-alanine	100 mg
L-arginine	100 mg
L-glycine	100 mg
L-histidine	100 mg

L-isoleucine	100 mg
L-phenylalanine	50 mg
L-threonine	50 mg
L-serine	100 mg

12. The supplement of claim 8, in unit dosage form, comprising:

Propionyl L-carnitine	250 mg
Acetyl L-carnitine	250 mg
Isovaleryl L-carnitine	250 mg
L-carnitine	250 mg
Ribose	1 g
Glucose-1,6-diphosphate	200 mg
Fructose-1,6-diphosphate	200 mg
Galactose-1,6-phosphate	200 mg
Glycerol-3-phosphate	200 mg
Phosphoenolpyruvate	100 mg
Thiamine pyrophosphate	5 mg
Pyridoxal-5-phosphate	5 mg
Magnesium stearate	2 mg

13. The supplement of claim 8, in unit dosage form, comprising:

Propionyl L-carnitine	250 mg
Acetyl L-carnitine	250 mg
Isovaleryl L-carnitine	250 mg
L-carnitine	250 mg
Ribose	1 g
Vit. A	1250 U.I.
Vit. B ₁	0,5 mg
Vit. B ₆	30 mg
Vit. C	50 mg
Vit. E	5 mg
Nicotinamide	25 mg
Vit. B ₁₂	100 mcg
Vit. D	100 U.I.

Pantothenic acid	30 mg
Magnesium glycinate	5 mg
Manganese	1 mg
L-Selenomethionine	50 mcg
Molybdenum	10 mcg
Zinc	1 mg

14. A method for the prevention and/or treatment of states of myocardial or skeletal muscle dysfunction related to conditions of anoxia or insufficient energy supply as occurring in coronary or post-infarct disorders or during prolonged physical activity and muscle fatigue, which comprises administering to an individual in need thereof a combination composition comprising the following ingredients:

- (a) an alkanoyl L-carnitine selected from the group comprising isovaleryl L-carnitine, propionyl L-carnitine or the pharmacologically acceptable salts thereof or mixtures thereof; and
- (b) ribose or a phosphorylate derivative thereof.

INTERNATIONAL SEARCH REPORT

In: **onal Application No****PCT/IT 01/00283****A. CLASSIFICATION OF SUBJECT MATTER****IPC 7 A61K31/70 A23L1/305 A23L1/09 A23L1/236 A23L1/302**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, FSTA, BIOSIS, CHEM ABS Data**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 65476 A (BIOENERGY INC ;ST CYR JOHN (US); JOHNSON CLARENCE A (US)) 23 December 1999 (1999-12-23) claims 1-5,7,9-16; example 7 page 3, line 28 -page 4, line 2,20-25 page 5, line 16 -page 6, line 18	1-14
A	WO 88 01861 A (BAXTER TRAVENOL LAB) 24 March 1988 (1988-03-24) page 4, line 1-19 page 5, line 27 -page 6, line 3 page 6, line 18 -page 11, line 11 claims 1,3,5,8,9,12,17,18,23,32; tables 1,2	1-14
A	EP 0 652 012 A (NAITO ALBERT) 10 May 1995 (1995-05-10) claims 1,3,6,9; example 3	1-14
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/IT 01/00283

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 15488 A (BUECHEL JUTTA ;TECHNOLIZENZ ETS (LI)) 21 July 1994 (1994-07-21) claims 1,2,8,9,13-15; table 1 page 3, line 8 -page 4, line 14 page 4, line 30 -page 5, line 9 page 5, line 26 -page 6, line 4 -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/IT 01/00283

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 14

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy